Message

From: Henry, Tala [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=8BFC0A617A4A43BAA8856541C70622BE-THENRY02]
Sent: 10/1/2021 12:04:10 PM
To: Todd Stedeford [tstedeford@lawbc.com]
Subject: FW: New submission to your Research Topic - (787756)

Can we talk about this briefly after we talk to Annie?

Tala R. Henry, Ph.D.
Deputy Director
Office of Pollution Prevention & Toxics

T: 202-564-2959
E: henry.tala@epa.gov

From: Frontiers in Toxicology Editorial Office <toxicology.editorial.office@frontiersin.org>
Sent: Friday, October 1, 2021 2:23 AM
To: Todd Stedeford <todd.stedeford@gmail.com>
Cc: Claire Terry <claire.terry@corteva.com>; Carole Hirn <carole.hirn@jti.com>; Henry, Tala <Henry.Tala@epa.gov>; Andreas Stucki <andreass@thepsci.eu>; Amy Clippinger <amyjc@piscltd.org.uk>
Subject: New submission to your Research Topic - (787756)

Dear Dr Stedeford and co-Topic Editors,

A new manuscript titled "Evaluation of inhalation exposures and potential health impacts of ingredient mixtures using in vitro to in vivo extrapolation" has been submitted to Frontiers in Toxicology, section In Vitro Toxicology and linked to the Research Topic: Chemical Testing Using New Approach Methodologies (NAMs).

You have been selected by the authors as the preferred handling editor. If you have a conflict of interest with the authors or the work presented (see policy at https://www.frontiersin.org/about/review-system#EditorialPolicies) or if you are currently unavailable, please reassign the manuscript to a co-Topic Editors directly from the Review Forum or inform us immediately in response to this email.

The next step is for you to perform a preliminary check to ensure that the manuscript is suitable for review. Please complete this check within 7 days. If it contains technical or ethical issues, or if it is below the standards of the field and can't be sufficiently improved, you should recommend it for rejection to the Chief Editor.

If you believe the manuscript to be out of scope of the section/journal it has been submitted to, you can recommend a transfer to another section/journal from the Review Forum. Alternatively, should you find the manuscript to be outside of the scope of the Research Topic, please contact the editorial office immediately by replying to this message. This must be done within the next six days to prevent an unsuitable manuscript from being sent out for review.

Otherwise, the manuscript should go out to reviewers for evaluation, and you should therefore invite suitable peer reviewers.

Please note that if 2 reviewers have not accepted your invitation within the next seven days, we will assist in finding suitable reviewers by matching the manuscript's keywords and scope with the expertise of our review editors and extend invitations through the system.

Should your co-Topic Editors be aware that you are unavailable at present, they can also directly take over the

assignment in the Review Forum via the link below:

https://review.frontiersin.org/review/bootstrap/8e444dca-b926-4652-b1ed-83177d82560b

Should any significant problems arise that cannot be addressed through direct discussion with the author, or if there is a substantial delay, please contact the editorial office.

Best regards,

Frontiers in Toxicology Editorial Office

Frontiers | Editorial Office - Collaborative Peer Review Team
www.frontiersin.org
Avenue du Tribunal Fédéral 34
Lausanne, Switzerland | T 41 21 510 17 60

For technical issues, please contact our IT Helpdesk (support@frontiersin.org) or visit our Frontiers Help Center (zendesk.frontiersin.org/hc/en-us)

Manuscript title: Evaluation of inhalation exposures and potential health impacts of ingredient mixtures using in vitro to in vivo extrapolation
Manuscript ID: 787756
Authors: Jingjie Zhang, Xiaoqing Chang, Tessa Holland, David Hines, Agnes Karmaus, Shannon Bell and K Monica Lee
Journal: Frontiers in Toxicology, section In Vitro Toxicology
Article type: Original Research
Submitted on: 01 Oct 2021
Research Topic: Chemical Testing Using New Approach Methodologies (NAMs)

Contribution to the field:
Fit-for-purpose in vitro to in vivo extrapolation (IVIVE) modeling approaches have been explored for individual chemicals in several case studies. However, there are few studies that investigate the application of IVIVE approaches for mixtures. Standardized approaches are currently not available for mixture IVIVE modeling, especially for complex mixtures such as tobacco smoke and e-vapor aerosols. In this study, we proposed, tested and compared multiple IVIVE approaches for mixtures, especially an outcome-oriented ingredient integration approach which consolidates the mechanism of in vitro bioactivity. We applied the IVIVE approaches to predict human exposures and potential health impact of inhaled chemical mixtures in e-cig aerosols. This work demonstrated the usefulness of NAMs to support toxicity and risk assessments of products and identify promising directions for future research.

Abstract: In vitro methods offer opportunities to provide mechanistic insight into bioactivity as well as human-relevant toxicological assessments compared to animal testing. One of the challenges for this task is putting in vitro bioactivity data in an in vivo exposure context, for which in vitro to in vivo extrapolation (IVIVE) translates in vitro bioactivity to clinically relevant exposure metrics using reverse dosimetry. This study applies an IVIVE approach to the toxicity assessment of ingredients and their mixtures in e-cigarette (EC) aerosols as a case study. Reported in vitro cytotoxicity data of EC aerosols, as well as in vitro high-throughput screening (HTS) data for individual ingredients in EC fluids (e-fluids) are used. Open-source physiologically based pharmacokinetic (PBPK) models are used to calculate the plasma concentrations of individual ingredients, followed by reverse dosimetry to estimate the human equivalent administered doses (EADs) needed to obtain these plasma concentrations for the total e-fluids. Three approaches (single actor approach, additive effect approach, and outcome-oriented ingredient integration approach) are used to predict EADs of e-fluids considering differential contributions to the bioactivity from the ingredients (humectant carriers [propylene glycol and glycerol], flavors, benzoic acid, and nicotine). The results identified critical factors for the EAD estimation, including the ingredients of the mixture considered to be bioactive, in vitro assay selection, and the data integration

approach for mixtures. Further, we introduced the outcome-oriented ingredient integration approach to consider e-fluid ingredients that may lead to a common toxicity outcome (e.g., cytotoxicity), facilitating a quantitative evaluation of in vitro toxicity data in support of human risk assessment.

Frontiers Review Guidelines

As a handling editor, it is important that you are familiar with the Frontiers Collaborative Review Guidelines, accessible at https://www.frontiersin.org/about/review-system. Briefly, the Frontiers review mandate is to evaluate the manuscript based on objective criteria, including the validity and rigour of the work.

Frontiers editors and reviewers are expected to abide by ethical standards in regards to conflicts of interest, confidentiality of the reviewed papers, objective evaluation of the work and preservation of reviewers anonymity until acceptance.